Implementation of VVM at a Vaccine Manufacturer

Part 2

Steps to VVM Implementation Part 2

1. WHO process
2. Receipt, Control and Storage of VVMs
3. Calibration of X-Rite 500 Series Spectrodensitometer
4. VVM Acceptance Testing
5. Application of VVM to Vials

Spectrodensitometer Daily Calibration and Annual Maintenance Program

- X-Rite 500 series spectrodensitometers are used to measure VVM active and reference surfaces
- Since the size of VVM is very small, specially-fabricated, very small apertures (2 mm) are required in the spectrodensitometer used for VVM
- Spectrodensitometers must be purchased from and serviced by Temptime to assure proper measurement capability
- Temptime pays for calibration by the spectrodensitometer manufacturer when required (every two years)
- Vaccine manufacturer is responsible for shipping charges
- Temptime provides notification when calibration is due and can also provide a “loaner” unit while the densitometer is out for calibration

VVM Acceptance Testing

- Vaccine manufacturers are responsible to develop SOPs related to VVM consistent with their quality system requirements
- SOPs for receiving, inspecting, storing and releasing of a lot of VVMs must be developed
- Some manufacturers rely solely on the Certificate of Analysis provided with a lot to support their release process
- Other manufacturers perform additional tests and verifications, including the 37°C water bath test as routine or on random lots
- These processes should suit the vaccine manufacturers' quality system and risk management practices

VVM Acceptance Testing - 37°C Water Bath

PLAY

Helpful Tips for Acceptance Testing Available

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VVM Acceptance Testing: Helpful Tips for Vaccine Manufacturers

Temptime understands that acceptance testing of VVMs is a critical part of many of our customers' quality systems. We are providing this list of helpful tips so we can share the benefits of our experience and expertise in testing VVMs. Temptime's test methods are based on the World Health Organization PQS Specification E06/IN05.2 and E06/IN05.VP.2. This list of tips is not a replacement for the specification but is additional information that will help our customers test VVMs in a consistent and compliant way.

- **Spectrodensitometer:** Temptime Corporation strongly recommends the use of an X-Rite 500 Series spectrodensitometer with special modifications made to the target by Temptime that allow the spectrodensitometer to be used effectively with VVMs. Temptime also provides the service and calibration of our customers' spectrodensitometers.
- **Optical Density Measurement:** Place VVMs with the release liner still attached on white card stock when measuring. The active indicator surface and label substrate are somewhat translucent, which allows the color of the testing surface below the indicator to affect the densitometer reading. White card stock eliminates this potential source of error. Temptime recommends using white, letter-size, 65 to 110 lbs. card stock with Cyan Optical Density ≤ 0.05 as measured with an X-Rite 500 Series Spectrodensitometer.

  The VVM consists of two parts, the Active Square, also called the Active Indicator or I, and the Reference Ring, also called the Ring or R. Measure the Optical Density of the VVMs by taking two optical density measurements from different points within the Active Square and two measurements from the Reference Ring: one on the bottom and another 90 degrees away from the first measurement. Refer to the diagram below.

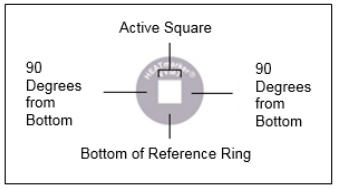

Figure 1. VVM Dot Measurement Targets

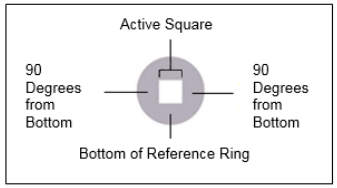

Figure 2. VVM Full Label Measurement Targets

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VVM 验收测试：疫苗生产厂商实用指引

Temptime 深知，VVM 验收测试是我们众多客户的质量体系的关键部分。我们提供该实用指引列表，旨在与大家分享我们在测试 VVM 方面的经验和技能优势。Temptime 的测试方法基于世界卫生组织制药业质量体系规范 E06/IN05.2 和 E06/IN05.VP.2。该指引列表并非用以替代规范，而是为客户提供额外的帮助信息，使其以规范、一致的方式测试 VVM。

- **光密度计：** Temptime 公司强烈推荐使用 X-Rite 500 系列光密度计，因为 Temptime 已对该系列光密度计的靶点范围进行特别改装，可有效配合 VVM 使用。Temptime 还为客户提供光密度计维修和校准服务。
- **光密度测量：** 在测量时，将仍贴有离型纸的 VVM 放置在白色的卡纸上。活性指示器表面和标签基底为半透明色，因此指示器下方的测试表面颜色会影响密度计读数。白色卡纸可帮助消除此类潜在的错误根源。Temptime 建议使用青色光密度≤ 0.05、65-110 磅的信纸大小的白色卡纸，与 X-Rite 500 系列光密度计配合测量。

  VVM 包含两部分：活性方块（亦称为活性指示器，简称“I”）和参照圆圈（简称为圆圈或“R”）。VVM 的光密度测量包括从活性方块中的不同点进行的两次光密度测量和从参照圆圈进行的两次测量：第一个点在底部，另外一个测量点与第一个测量点呈 90 度。请参考下图。

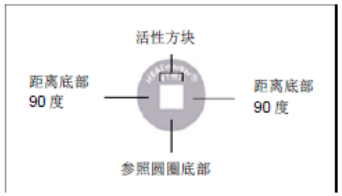


图 1. VVM 点测量靶点

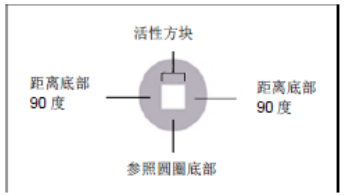


图 2. VVM 全标签测量靶点

Examples of Full Label VVM and VVM Dot

Full Label VVM - VVM Printed as Part of Vial Label

Sanofi Pasteur

20mm X 44mm

Double Size

GlaxoSmithKline

15mm X 57mm

Double Size

P.T. Bio Farma

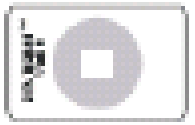
18mm X 48mm

Double Size

VVM Dot

10 mm

10mm X 16mm



VVMs are Supplied on Rolls 10,000 VVMs/roll

Full Label VVM

VVM Dot

VVMs are Applied During Final Labeling

- Preferred to apply VVM in line during final labeling operation
- Possible to apply VVM as a secondary process
- Ambient temperature and lighting (avoid excessive light exposure)
- Some manufacturers have local cold storage of VVM in labeling area

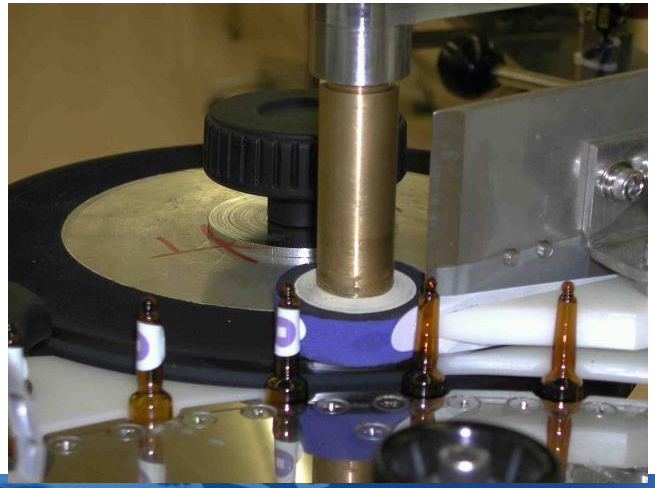
Kartoglu - WHO

VVM Dot Application to Cap of Vial or Neck of Ampoule

VVMs Dots are normally applied to the cap of the vial

YouTube Link to Serum Institute of India Video
http://www.youtube.com/watch?v=ytpS1SB_qGY

VVM Dot rectangles are applied to the neck of ampoules



VVM Application on Printed Label

The vaccine manufacturer can decide to apply the VVM dot onto the common label (printed locally) at his facility before the vial labeling.

Pre-printed Label

VVM Dot

Printed Label with VVM

VVM Application on Printed Label

2 Step Process

Crucell

1) VVM dot is applied to pre-printed common label with no VVM

Crucell

2) Common label with VVM is applied to vaccine vial

Automatic Label Application Equipment Suppliers

Several companies that are familiar with VVM application are:

- Accraply (Barry-Wehmiller Group)
- Bausch & Strobel
- Herma (Labelworx)
- Neri
- Maharshi Udyog and
- PharmaPack

Lesson Learned

Adhesion of VVM to cap strongly dependent on cap composition and texture

- Field complaint of poor adhesion of VVM to cap – VVMs lifting or coming off
  - Raised lettering on plastic cap and matte finish should be avoided
  - Best surface is flat and glossy (shiny)

- 2nd field complaint with different manufacturer
  - Cap changed and no test of adhesion performed prior to use

- No reported problems with metal caps. No other adhesion problems reported

Conclusions

- Successful GMP implementation of VVM at large and small vaccine manufacturers around the world independent of size of manufacturer
- VVM implementation by local manufacturers for local distribution in India and Indonesia
- SOPs (including training) must be put in place for receipt (IQA), storage and application of VVM
- Adhesion of VVM to cap must be verified
- Application of VVM to vials can be accomplished at room temperature by hand or by automatic equipment

Thank you!!!